Management of Graves' hyperthyroidism in pregnancy: focus on both maternal and foetal thyroid function, and caution against surgical thyroidectomy in pregnancy

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Abstract
Graves' disease is a common autoimmune disorder in women in fertile ages. The hyperthyroidism is caused by generation of TSH-receptor activating antibodies. In pregnancy both the antibodies and the antithyroid medication given to the mother pass the placenta and affect the foetal thyroid gland. Thyroid function should be controlled not only in the mother with Graves' hyperthyroidism but also in her foetus. The review includes two cases illustrating some of the problems in managing Graves' disease in pregnancy.

Major threats to optimal foetal thyroid function are inadequate or over aggressive antithyroid drug therapy of the mother. It should be taken into account that antithyroid drugs tend to block the foetal thyroid function more effectively than the maternal thyroid function, and that levothyroxin (L-T4) given to the mother will have only a limited effect in the foetus.

Surgical thyroidectomy of patients with Graves' hyperthyroidism does not lead to immediate remission of the autoimmune abnormality, and the combination thyroidectomy + withdrawal of antithyroid medication + L-T4 replacement of the mother involves a high risk of foetal hyperthyroidism.

Conclusion: Antithyroid drug therapy of pregnant women with Graves’ hyperthyroidism should be balanced to control both maternal and foetal thyroid function. Surgical thyroidectomy of a pregnant woman with active disease may lead to isolated foetal hyperthyroidism.

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Introduction
Graves’ disease is a common autoimmune disorder that may have diverse clinical manifestations. The key pathogenetic element is autoimmunity against the TSH receptor (1), and the most common clinical abnormality is hyperthyroidism caused by TSH-receptor stimulating autoantibodies.

In populations with sufficient iodine intake Graves' disease is the most common cause of hyperthyroidism (2), and ~1% of pregnant women have been treated before, or are being treated during pregnancy for Graves' hyperthyroidism.

Appropriate management of Graves' disease during the pregnancy is important for the mother's health and for the course of pregnancy. Moreover, the quality of management may have considerable impact on the progeny both in foetal and in neonatal life and on the long-term health of the child.

The present mini-review discusses some of the important considerations in taking care of pregnant women with Graves’ disease. A special topic evaluated is the role of surgery with subtotal or total thyroidectomy in pregnant women with active disease.
On the other hand, if previous Graves’ disease has been treated surgically or with radiiodine, and whatever the current status, euthyroid with or without levothyroxin (L-T4) substitution, the pregnant woman may still harbour circulating antibodies against the TSH-receptor (TRAb). Hence, the foetus may be at risk for thyroid dysfunction because maternal antibodies pass the placenta (3).

Thyroid surgery for Graves’ disease is in most patients followed by a gradual disappearance of TRAb from circulation (similar to the effect of therapy with antithyroid medication), whereas radiiodine therapy is often followed by an immediate worsening of autoimmunity with an increase in TRAb in serum (6–8). The duration of this worsening is about 1 year, and it is normally followed by a subsequent gradual fall in the levels of TRAb in serum. However, even 5 years after radioiodine therapy many patients are still TRAb positive (8).

Thus, depending on the serum level of TRAb, it may be relevant to advise women to postpone pregnancy for more than the usual 4–6 months (for reason of radioprotection) after radioiodine therapy to prevent the risk of thyroid dysfunction in the foetus. Even if the risk of high TRAb in the mother is in general lower after thyroid surgery than after radioiodine therapy (8), similar considerations may be relevant after surgical thyroidectomy for Graves’ hyperthyroidism.

**Risks and complications from Graves’ hyperthyroidism and therapy in the pregnant woman**

Table 1 gives an overview of some complications associated with untreated Graves’ hyperthyroidism in pregnant women as well as some of the consequences of the different types of therapy. The physical burden of untreated or inadequately treated hyperthyroidism added to the burden of pregnancy may precipitate congestive heart failure in the mother, and pre-eclampsia is a common phenomenon in hyperthyroid pregnant women (9, 10). In severe cases, thyroid storm may develop (9–11). Such complications and more direct effects of excess thyroid hormone lead to a high risk of miscarriage, placental abruption and preterm delivery if a pregnant woman is hyperthyroid (12). Accordingly, a primary goal of therapy of Graves’ hyperthyroidism in a pregnant woman is to avoid complications to hyperthyroidism in the mother by making and keeping her euthyroid or near euthyroid.

Among the three common types of therapy of Graves’ hyperthyroidism, antithyroid medication (propylthiouracil (PTU)), methimazole or its prodrug carbimazole), thyroid surgery and radiiodine therapy, the latter is not useable in pregnant women because of the foetal irradiation.

The two therapeutic modalities, antithyroid medication and surgery, can be used to make a pregnant woman euthyroid, but both types of therapy require special subsequent precautions in order to protect the foetus, as described below. In most instances, pregnancy is associated with a progressive decrease in the autoimmune activity of Graves’ disease (13, 14), so that in women receiving antithyroid medication for Graves’ hyperthyroidism before becoming pregnant it is often feasible to gradually reduce the dose or to withdraw the medication (14, 15). Occasionally, as reported in a few studies (16, 17), but not confirmed on a large scale (18), the nature of TRAb may change during pregnancy from stimulation to blocking of the TSH receptor. In such patients not only withdrawal of antithyroid medication, but also therapy of the mother with L-T4 may be necessary.

Antithyroid medication given as monotherapy is the first line of therapy of Graves’ hyperthyroidism in pregnancy. PTU is preferred, at least in the first trimester, because of the small increase in risk of malformations associated with the use of methimazole (19–21). As discussed below and illustrated by the two cases presented, focus on keeping the dose of medication as low as possible is important to protect the foetus against hypothyroidism.

A special case is represented by women who receive L-T4 replacement therapy after a previous radiiodine therapy or surgical thyroidectomy for Graves’ hyperthyroidism (Table 1). Such women will often need an increase in the dose of L-T4 in early pregnancy, as will other women treated for hypothyroidism (22).

**Risks and complications from Graves’ hyperthyroidism and therapy in the foetus**

Thyroid hormones are necessary for optimal mammalian foetal and neonatal development, and the risk of malformations may be increased in the newborns to hyperthyroid mothers (23, 24). Lack of thyroid hormones for more than a few weeks during vulnerable periods of development involves a risk of permanent cerebral impairment (25). On the other hand, excess amounts of thyroid hormones may lead to growth retardation and accelerated bone maturation, and it is associated with an increase in the risk of foetal death (26). In the brain, local concentrations of thyroid hormone are among other factors dependent on the activity of thyroid hormone activating and inactivating deiodinases. Somewhat unexpected, studies of experimental animals have revealed that congenital defects in the activity of thyroid hormone inactivating enzymes are much more deleterious for normal development and function of the CNS pituitary–thyroid axis than the lack of activating enzymes (27).

Thus, it is important when treating Graves’ hyperthyroidism in a pregnant woman to focus on keeping physiological amounts of thyroid hormones not only in the maternal but also in the foetal compartment. In the later part of pregnancy, foetal thyroid function can be
studied directly by performing thyroid function tests on blood obtained by cordocentesis (28). However, cordocentesis carries a 1–2% risk of foetal loss (29), and in the vast majority of women it is possible to judge foetal thyroid function with sufficient precision without having to perform cordocentesis. Table 1 shows how the foetus may be affected by Graves’ hyperthyroidism in the mother and by therapy, and Table 2 shows some of the factors that are important for the balance between maternal and foetal thyroid function in Graves’ hyperthyroidism.

The importance of normally not using block-replacement therapy (PTU + L-T4) after week 10–12 of pregnancy as indicated in Tables 1 and 2 is illustrated by the following email received August 2008 from a Dutch woman who had found a previous discussion of management of Graves’ disease in pregnancy on the internet:

Dear Mr Laurberg,

Before my pregnancy I was diagnosed with hyperthyroidism. My doctor prescribed PTU three times 100 mg daily and T4. During my pregnancy the treatment remained the same. My values of TSH and T4 were very good. I did have my doubts about the high dosage of PTU, but he assured me that it was just fine.

My daughter was born in September 2007. She was born with severe hypothyroidism, a large struma and an MRI showed a lot of fluid in her brain. We were in shock.

She is now doing very well, but we have a feeling that her condition was caused by my high doses of PTU. Is that possible?

Kind regards,

XXX

This is the experience of a patient, and the authors have had no access to the files of the patient.

Stimulating TSH-receptor antibodies leading to Graves’ hyperthyroidism in the pregnant woman pass the placenta, as do thyroid hormones to a limited degree, and in general, if the mother suffers from untreated Graves’ hyperthyroidism it can be assumed that the foetus is hyperthyroid.

Antithyroid drugs also pass the placenta, and therapy of the maternal hyperthyroidism is also therapy of the foetal hyperthyroidism. However, antithyroid drug therapy tends to be more effective in the foetus than in the mother (15). Accordingly, when the mother is euthyroid on antithyroid drug therapy it is important to be aware of the risk for foetal hypothyroidism (Table 1) as illustrated by case 1.
Table 2  Graves’ hyperthyroidism in pregnancy and the balance between maternal and foetal thyroid function.

i) TSH-receptor stimulating antibodies produced in the mother and inducing maternal hyperthyroidism pass the placenta, and they stimulate the foetal thyroid  
ii) If the mother has an intact thyroid, her thyroid function mirrors the thyroid function of the foetus  
iii) Antithyroid drugs (propylthiouracil and methimazole) pass the placenta and induce a block of both the maternal and the foetal thyroid hormone production  
iv) At a given dose of propylthiouracil or methimazole the block of the foetal thyroid is more effective than of the maternal thyroid  
v) During antithyroid drug therapy the thyroid function of the mother should be kept around or slightly above upper normal to avoid foetal hypothyroidism in the last part of pregnancy  
vi) Thyroid hormones only pass the placenta barrier to a very limited degree  
vii) A combination of antithyroid drug and L-T4 given to the mother to keep her euthyroid (block + replacement therapy) may mask foetal hypothyroidism induced by the antithyroid drugs  
viii) The combination of block (of the foetal thyroid) and L-T4 given to the mother to keep her euthyroid (block + replacement therapy) may mask foetal hypothyroidism induced by the antithyroid drugs  
ix) Appropriate dosing of antithyroid drugs to keep the foetus euthyroid in an athyreotic mother with active Graves’ disease is difficult, and the situation is best avoided if possible

Case 1

A 29 year-old woman had repeated episodes of relapsing hyperthyroidism since the age of 13 years. She had been on and off antithyroid drugs several times, but the thyroid function had been stable on antithyroid drug therapy for the last 2 years. During the current uncomplicated pregnancy the patient received therapy with PTU 100 mg × 4/day and was euthyroid. At week 19 + 4 days of pregnancy foetal ultrasonography gave suspicion of a foetal goitre, and when ultrasonography was repeated at week 23, this revealed a rather large (7 ml) foetal goitre. Acute cordocentesis (week 23) showed a foetal serum TSH of > 200 mU/l (reference at week 20 around 3–4 mU/l (30, 31)) and L-T4 (50–100 μg) was administered into the maternal amniotic fluid on a total of four occasions over 1 month. At the time of the cordocentesis, the mother had a serum TSH of 2.5 mU/l (reference 0.3–4.5 mU/l), total T4 was 75 nmol/l (reference: 90–210 nmol/l at this phase of pregnancy), total tri-iodothyronine (T3) was 2.7 nmol/l (reference: 1.8–4.0 nmol/l at this phase of pregnancy). She was clinically euthyroid, but she had a large goitre (171 ml by ultrasonography) with some vascular sounds. There were no measurable TSH-receptor antibodies in serum (<0.3 U/l, reference <1.0 U/l, DYNOtest TRAK human, BRAHMS, Berlin, Germany). Based on the assumptions that the foetal hyperthyroidism and goitre were caused by the relatively high dose of PTU given to the mother, that the maternal Graves’ disease was in remission, and that the relative resistance of the mother to PTU was caused by her large amount of thyroid tissue, the dose of PTU was reduced from 400 to 50 mg/day, and at week 32 of pregnancy PTU was withdrawn. At week 32 the maternal serum TSH was 0.3 mU/l, total T4 was 143 nmol/l, total T3 was 3.5 nmol/l and the maternal goitre size had decreased to 127 ml. The foetal goitre disappeared. At delivery (week 40) cord serum TSH was normal (5.4 mU/l) and serum TSH in the neonate at day 5 was 3.0 mU/l.

Four months after the delivery the mother had clinical and biochemical relapse of Graves’ hyperthyroidism and TRAb increased to 26 U/l. After a course of antithyroid drug therapy + potassium iodide for 10 days, surgical total thyroidectomy was performed with the removal of 401 g goitre.

Apparently, too little attention had been paid to the absence of TRAb and also to the lack of increase in serum T4 during the first half of pregnancy in this patient. In the early part of pregnancy serum total T4 and total T3 increase gradually in parallel with the increase in serum thyroid hormone binding globulin (32). As a practical measure, the reference ranges for total T4 and T3 can gradually be adjusted from week 7 to 16 of pregnancy with an increase in both low and high limits of reference with 5% of non-pregnant values per week. After week 16, the reference ranges are ~50% higher than non-pregnancy ranges until delivery (32). It may be speculated that the low serum T4 in the mother contributed to the high-foetal serum TSH, but the main factor is undoubtedly blocking of the foetal thyroid by PTU.

Case 1 illustrates the importance of trying to reach the minimal dose of antithyroid drugs during pregnancy and to stop medication whenever it is possible provided serum TSH in the mother is not low, and especially if the mother becomes TRAb negative. In case 1, the foetal goitre was caused by excessive foetal TSH secretion in response to drug induced foetal hypothyroidism. Many similar cases have been published (33–42), and often it is not necessary to perform cordocentesis to make the diagnosis.

Case 2 is a more complicated patient where both maternal TRAb and foetal TSH may have participated in the generation of foetal goitre, and where measurement of TSH in cord blood obtained by cordocentesis was necessary to differentiate the two causes of foetal goitre.

Case 2

A 29 year-old woman had new Graves’ disease with hyperthyroidism, mild orbitopathy and diffuse goitre
diagnosed at week 19 of pregnancy. Therapy with PTU (initial dose 100 mg × 3/day) + propranolol led to clinical and biochemical normalization. At gestational week 29, serum TSH and fT₄ being in the normal range, therapy was inadvertently withdrawn. Resumption of hyperthyroidism occurred a few weeks later. At week 32, after 1 week of PTU therapy (50 mg × 3/day) serum fT₄ was 30.7 pmol/l (reference 10–26 pmol/l), fT₃ was 22.9 pmol/l (reference 3–7 pmol/l) and TSH was <0.05 mU/l (0.5–4.8 mU/l). Maternal TRAb was high at 99 U/l (reference <10 U/l, TRAK assay, BRAHMS), and the thyroid stimulating activity was high (1396% of reference in a bioassay (43)). The dose of PTU was temporarily increased to 300 mg/day and subsequently fluctuated between 150 and 250 mg/day according to fT₄ and fT₃ levels.

Sonographic evaluations of the foetus had been normal, but at week 33 of gestation an enlarged foetal thyroid measuring 40×17 mm (maximal length × maximal width) was observed. One week later the goitre had increased, leading to cervical spine extension. Foetal biometry and activity were normal. Foetal heart rate was 142/min. Cordocentesis was performed at week 34 to further evaluate the cause of the goitre. Foetal thyroid function tests were: TSH 4.3 mU/l (normal for gestational age) (30, 31), fT₄ 4.0 pmol/l, fT₃ 3.1 pmol/l and tests in the mother showed TSH <0.05 mU/l, fT₄ 5.4 pmol/l, fT₃ 7.9 pmol/l. TRAb was 120 U/l in the mother and 60 U/l in the foetus. The dose of PTU was subsequently reduced to 150 mg/day, and this was continued throughout pregnancy. In the mother fT₃ normalized, and fT₄ remained low.

Repeated ultrasonographical investigations of the foetus showed further enlargement of the thyroid (week 36: right lobe 32×12, left lobe: 37×25 mm; week 39: right lobe 48×28, left lobe 40×21 mm) and at week 39 of gestation an uncomplicated caesarean section was performed. The newborn (weight 3970 g) presented normal except for a large goitre (neck circumference 24 cm). At the time of delivery, thyroid function tests in the mother were TSH <0.05 mU/l, fT₄ 4.4 pmol/l, fT₃ 6.7 pmol/l, and tests in the neonate (cord blood) were TSH 33.7 mU/l (reference in cord blood 2.5–25 mU/l (44, 45), fT₄ 2.2 pmol/l (10–18 pmol/l (44, 45)), fT₃ 4.1 pmol/l. TRAb was 62 U/l in the mother and 65 U/l in the neonate.

At day 6 the newborn showed signs of hyperthyroidism with tachycardia, hyperexcitability, erythema and mild cardiac failure. TSH was 0.9 mU/l, fT₄ was 23.5 pmol/l, fT₃ was 42 pmol/l. TRAb was 54 U/l and antithyroid drug therapy had to be instituted and maintained for 15 weeks.

After delivery, maternal PTU treatment was increased to 600 mg/day, and 3 months after a total thyroidectomy was performed with removal of 95 g goitre. The patient was well on L-T₄ replacement therapy and 3 years later she went through a pregnancy without complications.

In this case, the foetal goitre observed at week 34 of gestation was caused by TRAb stimulation, as TSH in the foetus was not elevated. On the other hand, the increase in foetal thyroid size in late pregnancy had probably been caused by a combination of stimulation by high levels of TRAb from the mother and elevated foetal TSH secretion. Evidently, the mother had Graves’ disease with a severe autoimmune disturbance, and it was difficult to balance therapy between maternal hyperthyroidism and foetal hypothyroidism.

Both cases illustrate the usefulness of a combined use of thyroid function testing including measurement of TRAb and ultrasonography of the foetus for monitoring of pregnancy in women with Graves’ disease. Ultrasonography of the foetus from mid-gestation is necessary for evaluation offoetal thyroid volume (Fig. 1) as well as foetal development in the women at risk of foetal thyroid dysfunction (40, 46). Women at risk are characterized by either the need of a high dose of antithyroid drug or the presence of high-serum levels of TRAb (42).

Figure 1 Ultrasonographical goitre in the foetus of case 2 in relation to Graves’ disease in the mother (A). For comparison a normal foetal thyroid in a normal pregnant woman is shown in (B). Courtesy of Dr Devonec.
The spectrum of management of severe Graves’ disease with predictable transplacental passage of thyroid stimulating antibodies

Before week 10–12, when the foetal thyroid hormone production becomes functioning, the transplacental passage of thyroid stimulating antibodies from the mother has no importance for thyroid hormone levels in the foetus. However, after week 12 the foetal thyroid will gradually develop to respond to the stimulation and the foetus may at some point become hyperthyroid, unless therapy is given.

If left untreated, the hyperthyroidism will be present at the time of birth, and it may last for several months because the maternal antibodies are only cleared slowly, half-life averaging 3 weeks, from the circulation of the neonate. The consequences of foetal and neonatal hyperthyroidism may be severe (Table 1).

If appropriate antithyroid drug therapy is given to the mother, this will keep the foetus euthyroid until birth. After birth the antithyroid drugs from the mother will disappear from the foetal circulation and thyroid within the first days, and after some delay, neonatal hyperthyroidism may develop until the maternal antibodies are cleared (26). High-serum levels of maternal TSH-receptor antibodies in late pregnancy indicate a risk of neonatal hyperthyroidism (3). This complication is illustrated in case 2.

During the period of foetal and neonatal hyperthyroidism the pituitary TSH secretion has been suppressed and the phase of neonatal hyperthyroidism may be followed by a phase of secondary hypothyroidism, until pituitary TSH secretion is restored (47).

If the pregnant woman has previously received ablative treatment for Graves’ hyperthyroidism by thyroid surgery and especially by radiiodine as discussed above, the mother may still be producing thyroid stimulating antibodies (8). A test for the presence of TRAb in serum should be performed before the second half of pregnancy (3). If positive, the foetus should be followed carefully for signs of thyroid dysfunction.

Case 2 illustrates the difficulty of balancing antithyroid medication in a pregnant patient with active disease. In such a patient, surgical thyroidectomy in the second trimester of pregnancy might be considered, as has been recommended in women who need persistently high doses of antithyroid drugs to control Graves’ hyperthyroidism (48).

There is little published evidence to indicate whether the recommended strategy of thyroid surgery (48) is optimal or not, and accordingly no evidence-based recommendations can be given. However, TRAb disappears slowly after surgical thyroidectomy, with only about half of the patients being TRAb negative after a year (8). This means that even if the pregnant woman becomes euthyroid after surgery + withdrawal of antithyroid medication + l-T4 administration, the foetus may be hyperthyroid from maternal TRAb. In one of the published cases of isolated foetal hyperthyroidism, the mother had undergone thyroid surgery for Graves’ disease only 2 months before becoming pregnant (49), thus coming close to the situation of thyroidectomy during pregnancy.

Thus, we recommend that surgical thyroidectomy of a pregnant woman with Graves’ disease is only performed in case of uncontrollable hyperthyroidism that threatens the health of the woman, or when antithyroid drugs are not tolerated. If thyroidectomy is performed, this should be followed by a systematic and careful follow-up evaluation of the thyroid state of the foetus.

In case of isolated foetal hyperthyroidism after thyroid ablation in the mother, this might be treated by administering antithyroid medication to the mother in combination with the l-T4 replacement started after the ablation. The experience with such therapy is limited and a close monitoring of the foetus is necessary. In a review of 11 anecdotal reports of antithyroid drug therapy given to mothers for isolated foetal hyperthyroidism, all the mothers had received ablative therapy for Graves’ hyperthyroidism before becoming pregnant (50). Outcomes were better after therapy than in pregnancies where these women had not been treated with antithyroid drugs. Future results of prospective monitoring and therapy of foetal hyperthyroidism after maternal thyroidectomy during pregnancy should be published to accumulate experience and evidence.

In conclusion, thyroid function should be controlled not only in the pregnant woman with Graves’ hyperthyroidism but also in her foetus. This is necessary to diminish the risks to the mother, to increase the likelihood of a successful outcome of the pregnancy, and to minimize the risk to the child. Recent studies have suggested that children born of inadequately treated hyperthyroid mothers have a risk of more prolonged, maybe even permanent developmental disruption of hypothalamic–pituitary–thyroid function (51, 52), that may correspond to the developmental abnormalities observed in animals with lack of type 3 deiodinase (27). Insufficient or over aggressive antithyroid drug therapy of the mother or a failure of recognizing and treating TRAb-induced foetal hyperthyroidism in a mother with no functional thyroid gland are major threats to optimal foetal thyroid function.

Declaration of interest

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